

# A Practical Approach to Screening Psoriasis Patients for Therapy with Biologic Agents

by Joshua A. Zeichner, MD

## Abstract

The use of biologic agents for the treatment of psoriasis and psoriatic arthritis is increasingly growing among dermatologists. Proper screening is crucial to select patients who are appropriate candidates for these drugs. This article will outline a practical approach to evaluating patients, focusing on key aspects of the medical history, physical examination, and laboratory testing.

## Introduction

Psoriasis is a chronic, inflammatory condition that affects roughly two percent of the United States population.<sup>1</sup> It is a systemic disease that manifests most prominently in the skin as well-demarcated, erythematous, scaly plaques. Involvement may range from an isolated plaque to greater than 90 percent body surface area in some patients. Additionally, psoriasis may be associated with joint disease. While mild cases often respond to topical treatment, patients with extensive disease may require systemic drugs. As the armamentarium of systemic

therapies for psoriasis continues to grow, it is important for providers to understand fully how to prescribe these agents and appropriately monitor their patients.

## Background on Biologic Agents

The biologic agents as a class of drugs may be defined as pharmacologically active proteins that are developed through recombinant DNA technology.<sup>2</sup> Currently, five of these drugs are approved by the Food and Drug Administration (FDA) for the treatment of psoriasis and/or psoriatic arthritis. Several newer agents are in various stages of development and clinical trials. Since their introduction, the use of biologics has grown significantly. While the cost of these prescriptions is higher than traditional systemic immunosuppressive agents, total healthcare costs have not been affected, and patients have shown better adherence rates compared to other therapies.<sup>3</sup> The biologic agents are safe and efficacious, but are not without potential complications.<sup>4</sup> With proper selection and monitoring of patients, dermatologists can

confidently prescribe these medications.

Biologics may be broadly divided into either tumor necrosis factor alpha (TNF- $\alpha$ ) or T-cell lymphocyte inhibitors. These drugs work at different steps along the same pathway of immune dysregulation that leads to psoriasis. The three approved TNF inhibitors are etanercept (Enbrel, Amgen, Thousand Oaks, California), adalimumab (Humira, Abbott Laboratories, North Chicago, Illinois), and infliximab (Remicade, Centocor, Malvern, Pennsylvania). Etanercept is a fusion protein comprising the p75 TNF-receptor subunit with the Fc portion of human immunoglobulin G (IgG). It is administered as a weekly subcutaneous injection and competitively binds TNF- $\alpha$  and blocks endogenous TNF- $\alpha$  from binding to cell surface receptors.<sup>5</sup> Etanercept received FDA approval for psoriatic arthritis in 2002 and psoriasis in 2004. Adalimumab is a fully humanized, monoclonal antibody that binds TNF- $\alpha$  and prevents binding to cell surface TNF-receptors. It is a subcutaneous injection given every other week<sup>6</sup> and was approved for psoriatic arthritis in 2003 and psoriasis in 2008. Infliximab is an intravenous infusion administered approximately at monthly intervals. It is a chimeric, monoclonal antibody to TNF- $\alpha$  comprising a murine-antigen binding site and a human IgG constant site.<sup>7</sup>

Psoriasis is a T-cell mediated disease, and the second class of biologic agents directly targets these pathogenic cells. Alefacept (Amevive, Astellas Pharma US, Inc., Deerfield, Illinois) is a dimeric fusion protein combining IgG with lymphocyte function-associated antigen 3 (LFA-3). The drug binds the cluster of

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differentiation 2 (CD-2) receptor on the surface of T-cell lymphocytes, which leads to T-cell apoptosis.<sup>8</sup> Alefacept received FDA approval for psoriasis in 2003. The second drug in this category is efalizumab (Raptiva, Genentech, South San Francisco, California)—a humanized, monoclonal antibody targeting CD11a, a subunit of LFA-1—which inhibits its binding to ICAM-1 on the endothelial cell surface.<sup>9</sup> Therefore, lymphocytes are unable to migrate from the blood vessels to the skin. In 2003, efalizumab was approved for the treatment of psoriasis.

### Selecting Patients for Biologic Agents

Clinicians must carefully screen patients to assess whether they are appropriate candidates for biologic agents. There is no single guideline to follow, and prescribers vary greatly in their practices.<sup>10</sup> In a recently published, in-depth literature review evaluating the evidence for many common screening and monitoring tests in patients on biologics, the authors were unable to make definitive recommendations either in favor or against them.<sup>11</sup> Several consensus statements have also been published to reconcile differences among dermatologists and provide recommendations for care of patients on biologics.<sup>2,12,13</sup> While there is no correct way to take care of these patients, below is a practical way to approach the psoriasis patient in whom you may start a systemic biologic therapy. Figure 1 summarizes the key points to cover in screening a potential patient for therapy with a biologic agent. Prior to initiating any biologic agent, it is important to obtain a baseline evaluation of a patient, including a thorough medical history and physical examination. Key elements of the medical history include a personal or family history of congestive heart failure (CHF),

#### Personal or Family History

- Demyelinating diseases, including multiple sclerosis
- Congestive heart failure
- Lymphoproliferative disease, including lymphoma
- Hematologic disorders
- Chronic infections, including hepatitis, HIV, persistent upper respiratory tract infections, indwelling urinary catheters, and chronic leg ulcers
- Skin or solid organ cancer

#### Laboratory Tests

- Comprehensive Metabolic Panel
- Complete Blood Count with Platelets
- +/- ANA
- +/- Hepatitis B and C Serologies
- +/- HIV Test
- PPD for tuberculosis (if positive, prophylactic treatment prior to biologic therapy)
- +/- Pregnancy test (for women of child-bearing potential)

**Figure 1.** Key points in screening patients for biologic therapies

demyelinating diseases such as multiple sclerosis, and any hematologic diseases. In addition, the clinician should determine whether the patient has signs or symptoms of arthritis, as this will determine which biologic agent is selected for the patient. Particular attention should be paid to the lymph nodes, liver, and spleen to exclude a potential lymphoreticular disease. Finally, patients should be given total body checks before starting a biologic agent in search of any skin cancers.

These highlighted aspects of the medical history and physical examination are contraindications to starting some biologic agents. There have been reports of exacerbation of and new-onset CHF<sup>14,15</sup> and demyelinating diseases<sup>16–19</sup> in patients on TNF blockers. The association between TNF inhibitors and the development of lymphoproliferative disorders and other malignancies,

such as squamous cell carcinomas of the skin, remains unclear.<sup>20–24</sup> Patients with non-melanoma skin cancers should be treated cautiously with TNF inhibitors. Those with a personal or family history of lymphomas should not be treated with biologics. Patients with a history of any solid tumors should be counseled to avoid biologics, as their risks are unknown.

Baseline laboratory studies should be performed and evaluated prior to initiating therapy with a biologic agent. These tests should include a comprehensive metabolic panel with liver function tests, a complete blood count with platelets, as well as a hepatitis panel. Baseline levels are important because hematologic and metabolic disturbances have been reported with these agents. All patients on alefacept develop a decrease in number of CD4+ lymphocytes, which should be monitored bi-weekly. The medication

should be held in patients whose CD4+ lymphocyte count drops below 250 cells/ $\mu$ L until the count rises above that threshold.<sup>8</sup> Efalizumab causes a leukocytosis, but can rarely lead to thrombocytopenia or an autoimmune pancytopenia, which must be closely monitored, initially on monthly intervals and then every three months with stable, continued therapy.<sup>9</sup> Liver toxicity has been reported in patients on biologics as well. Although isolated cases have occurred in patients on anti-T-cell agents, it is more common (yet still rare) when using the TNF blockers, especially infliximab. Various hematologic abnormalities, including anemia, have also been reported in patients on TNF inhibitors.<sup>5-7</sup>

Screening for an anti-nuclear antibody (ANA) prior to initiating a biologic agent has been controversial. While there is no official guideline, only a minority of practitioners check a baseline ANA prior to initiating therapy with a TNF blocker. A positive ANA is non-specific and should not, by itself, preclude a patient from starting a TNF blocker.<sup>11</sup> There are reports of patients developing positive ANA tests while on TNF blocker therapies, and the significance of this is still unclear.<sup>25,26</sup> Only rarely, however, do patients develop lupus-like syndrome. An association with TNF inhibitors is not definite, although some of the cases did resolve after discontinuation of the TNF blocker.<sup>27-31</sup> Therefore, ANA's should not necessarily be monitored on a regular basis, but rather evaluated only in patients with signs and symptoms of a lupus-like syndrome.

TNF- $\alpha$  is a cytokine that plays a crucial role in the development of granulomas, and therefore the response to and control of tuberculosis (TB) infections.<sup>32</sup> The Centers for Disease Control and Prevention (CDC) recommends

screening for tuberculosis prior to starting therapy with any TNF- $\alpha$  blocker. Providers should screen patients with a purified protein derivative (PPD) skin test prior to initiation of any biologic, but especially for the TNF blockers. The result of the PPD should be evaluated in the context of the patient's personal history, and in the case of a positive test, patients should have a full medical work-up, including a chest radiograph.<sup>33</sup> In addition, a consult with an infectious disease specialist or pulmonologist should be considered. A positive PPD will not preclude a patient from starting a biologic agent. Two recent consensus statements addressing this issue have been published. The first was put out by the British Thoracic Society in 2005<sup>34</sup> and the second in 2008 in the *Journal of the American Academy of Dermatology*.<sup>35</sup> In both statements, the authors recommend that patients complete a full course of prophylaxis for latent TB prior to starting any immunosuppressive medication, including biologics as well as traditional agents.<sup>35</sup> However, in cases where patients urgently require systemic therapy for psoriasis, this therapy may be started after the patient completes two months of prophylaxis, provided they are compliant and tolerating the TB regimen well.<sup>34,35</sup> The CDC's preferred therapy for tuberculosis prophylaxis is isoniazid 5mg/kg (maximum of 300mg) daily for nine months, supplemented with vitamin B6.<sup>36</sup> It is important to note that in addition to anti-TNF therapy, chronic immunosuppression with other medications such as systemic steroids and methotrexate carries an increased risk for developing and reactivating TB as well.<sup>35</sup> Reactivation of TB has not been reported with use of efalizumab or alefacept.

Prior to initiating any immunosuppressive medication, including biologic agents, special attention should be paid to patients' vaccination status. Ideally, patients should receive vaccines prior to initiating therapy that will suppress the immune system, allowing a better response. Vaccines may be categorized into several different groups, including live-attenuated viruses, inactivated ("killed") viruses, toxoids, and subunit (acellular) polysaccharide antigen vaccines.<sup>4</sup> Live and live-attenuated viral vaccines are relatively contraindicated in patients on biologics or other immuno-suppressive agents, as there is a risk of reactivation of the virus. These vaccines include the measles, mumps, and rubella (MMR) vaccine as well as the oral polio vaccine and the varicella vaccine. Patients should be immunized for streptococcus (a subunit vaccine) and influenza (inactivated, viral vaccine). Patients should be vaccinated prior to initiating a biologic agent if possible, although the vaccines are still effective if given afterward.<sup>12</sup>

Other considerations to take into account prior to starting a biologic agent include the patient's age, sex, and immune status. The clinical trial data for the biologic agents in psoriatic patients have all been conducted in patients older than 18 years. However, one study shows safety and efficacy in a pediatric population of patients with psoriasis treated with etanercept.<sup>37</sup> There is minimal data on the use of biologic agents in pregnant patients. All of the biologic agents are pregnancy category B, with the exception of efalizumab, which is pregnancy category C. In animal reproduction studies, offspring of mice treated with efalizumab had a reduced ability to mount an antibody response at 11 weeks old, which partially reversed by 25 weeks.<sup>9,10</sup>

There are limited reports of the

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safety of biologic agents in patients with human immunodeficiency virus (HIV). Study subjects in the clinical trials for all the biologic agents were HIV negative. Currently, the package inserts for etanercept, adalimumab, and infliximab warn that these agents are contraindicated in patients with serious infections.<sup>5-7</sup> However, recent published cases report safe use of these TNF inhibitors in patients who were HIV positive.<sup>38,39</sup> These drugs did not influence CD4 counts or HIV viral load or increase morbidity or mortality. Additionally, they improved some of the symptoms of HIV, including cachexia, fatigue, and aphthous ulcers.<sup>40</sup> There are no randomized, placebo-controlled, clinical trials on the safety or efficacy of TNF inhibitors in HIV patients with rheumatic diseases published in the literature at this time. In addition, there are no reports of the use of the anti-T-cell agents efalizumab and alefacept in HIV-positive patients. Alefacept decreases the number of CD4-positive cells and is specifically contraindicated in HIV-positive patients in its package insert.<sup>8</sup> Similarly, efalizumab should not be given to patients with chronic or serious infections.<sup>9</sup>

Liver function should be assessed in all patients prior to starting a biologic agent, and when appropriate, hepatitis serologies should be performed. Reactivation of hepatitis B virus (HBV) has been reported in patients treated with infliximab<sup>12</sup> and etanercept,<sup>41</sup> and patients with HBV should not be started on a TNF-blocker. Unlike HBV, the anti-TNF agents have not been shown to exacerbate hepatitis C virus (HCV).<sup>39</sup> In fact, TNF- $\alpha$  blockade may actually be potentially beneficial in the setting of HCV, as TNF- $\alpha$  has been shown to be elevated in HCV patients and leads to liver fibrosis.<sup>42,43</sup> As is the case with obtaining ANA's, there is variability among providers' practices,

and each patient must be individually evaluated based on his or her clinical history.

## Conclusion

The biologic agents are a new option in the therapeutic armamentarium for treating patients with moderate-to-severe psoriasis and psoriatic arthritis. These drugs carry specific, potential side effects, and patients must be thoroughly screened to assess whether they are appropriate candidates for a biologic therapy. This screen should include close attention to the patient's past medical history as well as baseline laboratory testing.

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**Author: Dr. Zeichner is a Chief Resident, Department of Dermatology, Mount Sinai Medical Center, New York, New York. Section Editors: Jerry Tan, MD, FRCPC, is Adjunct Professor, University of Western Ontario, London, Ontario; President, Windsor Clinical Research Inc., Windsor, Ontario; and Consultant, Windsor Regional Hospital, Windsor, Ontario, Canada. He is also in private practice. Dr. Bhambri is a Dermatology Resident, UCLA Division of Dermatology, Los Angeles, California.**

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